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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/689,122	10/20/2003	Tabassum Naqvi	3817.14-1	4234

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EXAMINER	
HAQ, SHAFIQUL	
ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/689,122	NAQVI ET AL.	
	Examiner	Art Unit	
	SHAFIQUL HAQ	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-4 and 6-8 are pending and under active prosecution.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-4 and 6-8 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Sportsman et al. (US 6,806,053 B1) in view of Iwasaki et al. (J. Biol. Chem. 2002) and Hirata et al. (J. Biol. Chem. 1990).

Sportsman et al. in a cell-signaling assay of inositos-phospholipid signaling pathway, disclose detection of intermediate 1, 4, 5 IP_3 of the singnaling pathway. The assay include a tracer from the intermediate (i.e. tracer of 1, 4, 5 IP_3) and a specific binding partner for 1, 4, 5 IP_3 (intermediate) and the tracer (e.g. labeled 1,4, 5 IP_3). Sportsman et al. also disclose that the tracer may include a luminophore attached by a suitable chemistry to the intermediate (e.g. a fluorescein succinyl-labeled IP_3) (column 20, example 14 and figs. 5, 6, 7A, 7B, 8A and 8B). Sportsman et al. disclose that specific binding partner generally comprises any compound capable of specifically and competitively binding an analyte and an associated tracer and also disclose that fragments, derivatives or analogs of a preferred specific binding partner may be used (column 11, lines 22-35).

Sportsman et al., however, do not disclose IP_3R receptor or fragments thereof as specific binding partner in this assay.

Iwasaki et al. disclose IP_3R antagonists that strongly and specifically bind to IP_3 (analyte). Iwasaki et al. also disclose N-terminal ligand binding domain of mIP_3R1 comprising amino acid sequence 226-578 as the core region for high affinity binding to IP_3 and the binding affinity is approximately 1000 times greater than that of endogenous IP_3T (see page 2764, left column, lines 6-21).

Since a specific and a strong binding partner for IP_3 is disclose by Iwasaki et al., it would have been obvious at the time of the invention to a person of ordinary skill in the art to include core region of the IP_3R as taught by Iwasaki et al in the assay method of Sportsman to effectively measure IP_3 in a sample with a reasonable expectation of success because specific binding partner for IP_3 is envisaged in the method of Sportsman et al.

As for conjugate of IP_3 with a detectable label, Sportsman et al. disclose that the tracer may include a luminophore attached by a suitable chemistry to the intermediate (e.g. a fluorescein succinyl-labeled IP_3)(column 20, example 14) but, however, fail to disclose detectable label at the 2-hydroxy position of IP_3.

Hirata et al. disclose a series of 1,4,5-triphosphate (IP_3) analogs with substituents at 2 hydroxy position and disclose that such modification (substitution at 2-hydroxy position) do not substantially interfere with the affinity of IP_3 for IP_3 receptor (see abstract and page 8404, right column, lines 6-13).

Therefore, given the above fact that 2-hydoxyl position of IP3 can be substituted with organic groups without significantly affecting binding affinity of IP_3 for its binding partner (Hirata et al.), it would have been obvious at the time of the invention to a person of ordinary skill in the art to attach luminophore at the 2-hydroxy position of IP_3 in the IP_3-luminophore conjugate as suggested by Sportsman et al with a reasonable expectation of success because attachment by a suitable chemistry is disclosed by Sportsman et al. and substitution at the 2 hydroxyl position know for IP3, which does not affect IP3 binding affinity to its binding partner.

As for dependent claim 2, Sportsman et al. disclose that the assay may be homogeneous (column 9, lines 49-52). As for claims 4 and 6 Iwasaki disclose amino acid sequence 226-578 as the core region for high affinity binding to IP_3 and disclose a amino acids 224-604 of mouse IP3R fused to glutathione S-transferase to efficiently express the core region as a soluble active form (IP3 sponge) (page 2764, left column, lines 6-18) and as for claims 18-19, Sportsman et al. disclose component in a kit format (column 13, lines 34-35) and the packaging of components in kit form is a well-known obvious expedient for ease and convenience in assay performance and once a method has been established, one skilled in the art would clearly consider compiling in a kit format and change/modify different components of the kit to best suit the assay.

Response to Argument

4. Applicant's arguments and declaration under 37 CFR §1.132 filed 2/27/08 have fully been considered, but are not persuasive to overcome the rejection under 35 USC 103 as set forth in this office action of 12/13/07.

With regard to Hirata's reference, Applicants stated that what is reasonably taught by the example is that a homogenate of rat cerebellum--known to have IP_3R and many other receptors for other IP analogs--will bind to IP3 and derivatives at the 2-position of IP3 or the hydrolytic products thereof. The large number of available sites in the homogenate, the relatively low affinity that IP3 has for the different isoforms of IP_3R, and the possibility of modification of the IP3 and its analogs by enzymatic reactions, makes the data very difficult to analyze. Applicants also argued that Dr. Ullman's conclusions support the conclusion that there is insufficient evidence from the experimental data to conclude that the 2-position derivatives of IP are binding to the IP_3R. Applicants further asserted that Hirata does not support the conclusions that Hirata draws. The data are too ambiguous at best to draw conclusions that the 2-derivative of IP3 is binding to the various proteins. Without this showing, Hirata is inadequate to suggest the subject invention, that one can prepare a 2-derivative of IP3 and expect that it would bind to the IP3 receptor.

Applicants arguments and declaration under 37 CFR §1.132 have been fully considered but are not persuasive to remove Hirata as prior art because even if Hirata's data is not absolutely conclusive as asserted by Applicants', the data and Hirata's conclusion (see last 3 lines, second column of page 8407) that modification of second position of D-IP_3 reduced little the potential to interact with recognizable proteins provides a strong motivation to try the second position of D-IP3 for substitution. Hirata's data suggests that D-isomers substituted at 2-hydroxy position (i.e. D-209 and D-206) bind to IP_3 binding sites as Fig.6 shows that the D-isomers of both IP_3 analogs were capable of inhibiting the binding of D-[^{3}H]IP_3. D-[^{3}H]IP_3 binds to IP3 receptor and displacement of D-[^{3}H]IP_3 with the un-labeled IP_3 analog is indicative of binding of the un-labeled IP_3 analogs with IP_3 receptor present in cerebellum preparation. The statement by Applicants that the likely possibility that the inhibition is due to esterase catalyzed hydrolysis of D-206 and D-209 to D-IP3 without any clear supporting evidence is not persuasive.

Since, sponge protein comprises the core region (aa 224-604) of inositol 1,4,5-triphosphate receptor for IP3 binding (Iwasaki *et al*, page 2764, lines 6-25 of first column; see also lines 27-29, right column of page 2766, which discloses amino acid residues Arg-265, Lys-508 and Arg-511 in mouseIP_3 receptor are known to have a crucial role in IP3 binding) and strongly and specifically competed with endogenous 1,4,5-IP_3R for binding to IP_3 (Iwasaki et al. page 2763, left column, lines 13-17 and page 2764, lines 6-21), it would also be expected to bind 2 hydoxy substituted IP_3 analogs (substitution at 2 hydroxyl position) similarly to native IP_3R as show by

Hirata *et al*. Furthermore, if one is to prepare an IP_3 tracer (i.e. IP3 conjugated to a label) as suggested by Sportsman et al, and with the motivating disclosure in hand (i.e. substitution at 2 hydroxyl position does not reduce binding ability of the analog to interact with the receptor, Hirata et al), one of ordinary skill in the art would obviously first try the 2-hydroxyl position of IP3 to link the label.

Applicants are reminded that prior art is not limited just to the references being applied, but includes the understanding of one of ordinary skill in the art. The prior art reference (or references when combined) need not teach or suggest all the claim limitations. The "mere existence of differences between the prior art and an invention does not establish the invention's nonobviousness." The gap between the prior art and the claimed invention may not be "so great as to render the [claim] nonobvious to one reasonably skilled in the art." In determining obviousness, neither the particular motivation to make the claimed invention nor the problem the inventor is solving controls. The proper analysis is whether the claimed invention would have been obvious to one of ordinary skill in the art after consideration of all the facts. Factors other than the disclosures of the cited prior art may provide a basis for concluding that it would have been obvious to one of ordinary skill in the art to bridge the gap. The teaching, suggestion, or motivation test is flexible and an explicit suggestion to combine the prior art is not necessary. The motivation to combine may be implicit and may be found in the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. "[A]n implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a

whole, but when the 'improvement' is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Furthermore, one cannot show nonobviousness by attacking references individually wherein the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merk & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fines*, 837 F.2d 1071, 5USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.1992). In this case Sportsman et al. disclose an assay for detection of IP_3 which includes a tracer (tracer i.e. a labeled IP_3) and a specific binding partner for IP_3 and the tracer. Sportsman et al. also disclose that the tracer may include a luminophore attached IP3 (e.g. a fluorescein succinyl-labeled IP_3). Sportsman et al. disclose that specific binding partner generally comprises any compound capable of specifically and competitively binding an analyte and an associated tracer and also disclose that fragments, derivatives or analogs of a preferred specific binding partner may be used (column 11, lines 22-35). Therefore, Sportsman et al. disclose strong motivation to include IP_3 binding partners or fragments thereof in the assay methods. Iwasaki's reference is combined with Sportsman et al. because Iwasaki et al.

disclose a potential binding partner for IP_3 (i.e. IP_3 receptor or fragment of IP_3R) and disclose that N-terminal 226-578 amino acid sequence of mIP3R1 binds IP_3 with high affinity and thus would be obvious to try as a binding partner in the method as taught by Sportsman et al. for detection of IP3. Hirata's reference is combined with Sportsman because Sportsman et al. envisioned IP_3 tracer in the competitive immunoassay method (i.e. IP_3 labeled with a detectable molecule) and Hirata et al. disclose 2 hydroxyl position of IP_3 as a potential position for substitution with an organic group that do not substantially affect the affinity of IP_3 for IP_3 receptor and thus one of ordinary skill in the art would obviously try to link detectable molecules at that position (i.e. 2-hydroxyl position) as this position is a potential position for substitution that does not significantly interfere with binding to it's binding partner. Therefore, strong motivation is there to combine the references.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing

date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. The prior art made of record and not relied upon is considered pertiinent to applicant's disclosure.

Yoshikawa et al. (Biochem. Biophy. Res. Comm. 1999) disclose important region of binding domain of IP3 receptor for binding to IP3.

Riley et al. (J. Biol. Chem. 2002) disclose PEG linker at 2-hydroxyl position of IP3 more potent than IP3.

Morris et al. (Biochem. J. 2002) disclose that IP3 binding site lies within the N-terminal between residues 226 and 576 and the first 225 residues may inhibit IP3 binding.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shafiqul Haq whose telephone number is 571-272-6103. The examiner can normally be reached on 7:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shafiqul Haq/
Examiner, Art Unit 1641

/Long V Le/
Supervisory Patent Examiner, Art Unit 1641